Slope of the Instantaneous Hyperemic Diastolic Coronary Flow Velocity-Pressure Relation

A New Index for Assessment of the Physiological Significance of Coronary Stenosis in Humans

Carlo Di Mario, MD, PhD; Rob Krams, MD, PhD; Robert Gil, MD; Patrick W. Serruys, MD, PhD

Background Coronary flow reserve (CFR), the functional index of stenosis severity more frequently used in the catheterization laboratory, is greatly affected by the hemodynamic conditions at the time of measurement and cannot be applied in the immediate assessment of the outcome of coronary interventions. The aim of the present study was to establish the feasibility and reproducibility of the assessment of the slope of the instantaneous diastolic relation between coronary flow velocity and aortic pressure during maximal hyperemia (IHDVPS) using a spectral analysis of the intracoronary Doppler signal, to assess the sensitivity and specificity of this index in the detection of flow-limiting coronary stenoses in comparison with CFR, and to study the possibility of determining the zero-flow pressure from the intercept of the velocity-pressure relation on the pressure axis during a controlled cardiac arrest.

Methods and Results The instantaneous peak coronary flow velocity measured after intracoronary papaverine with a Doppler guidewire was plotted against the simultaneously measured aortic pressure, and the slope of the velocity-pressure relation in the phase of progressive diastolic velocity decrease was calculated during four consecutive beats. In nine normal arteries, a controlled diastolic cardiac arrest was induced by an intracoronary bolus injection of 3 mg adenosine. The IHDVPS could be assessed in 79 of 95 patients (83%), with a moderate intraobserver variability (0.4±11% after independent selection of different beats during maximal hyperemia). The IHDVPS showed no significant correlation with heart rate, mean diastolic aortic pressure, type of vessel studied, and cross-sectional area at the site of the velocity recording. The IHDVPS was significantly lower in arteries with ≥30% diameter stenosis than in normal or near-normal arteries (0.71±0.48 versus 1.73±0.80 cm·s⁻¹·mm Hg⁻¹, P<.0000002). In the stenosis group, both IHDVPS and CFR were significantly correlated with the minimal luminal cross-sectional area (r=.46, P<.05 and r=.62, P<.002, respectively). The study of the velocity-pressure relation during long diastolic pauses showed a curvilinear relation between velocity and pressure in the lower pressure range, with an upward concavity to the velocity axis and no intercept with the pressure axis in most cases.

Conclusions The IHDVPS can distinguish between arteries with and without coronary stenoses and has a significant inverse correlation with the severity of the stenosis. Under the stable hemodynamic conditions of this study, the IHDVPS and CFR had similar sensitivities and specificities in distinguishing normal and stenotic vessels and demonstrated similar correlation with minimal luminal cross-sectional area. The curvilinearity of the velocity-pressure relation during long diastolic pauses, possibly due to a significant reduction of luminal cross-sectional area at low pressures, complicates the use of the flow velocity-pressure relation for the assessment of the zero-flow pressure. (Circulation. 1994;90:1215-1224.)

Key Words • flow • Doppler ultrasound • circulation

Coronary flow reserve (CFR) is the index commonly used as a physiological alternative to measurements of stenosis geometry in the assessment of coronary stenosis severity. However, CFR correlates with the stenosis severity defined with angiography only in very selected subsets of patients and is influenced by changes in resting myocardial flow and by the hemodynamic conditions at the time of assessment and is unable to provide an immediate assessment of the results of coronary interventions.

To overcome these limitations of CFR, Mancini et al. proposed the assessment of the instantaneous relation between aortic pressure and coronary flow during maximal hyperemia in the phase of progressive flow decrease in mid- and end diastole. In four separate series of experiments, the slope of the instantaneous hyperemic diastolic flow-pressure relation was shown to be independent of changes in heart rate, preload, aortic pressure, and cardiac contractility and well correlated with the severity of coronary stenoses and the maximal subendocardial conductance measured using radiolabeled microspheres. Intracoronary Doppler can accurately measure instantaneous changes of flow velocity during the cardiac cycle and using Doppler-tipped guidewires, the velocity measurements can be obtained distal to the stenosis, so that the flow velocity changes will certainly reflect the severity of the lesion under study.

Accordingly, the purpose of the present study was to assess the feasibility and reproducibility of the measurements of the slope of the instantaneous hyperemic diastolic flow velocity-pressure relation (IHDVPS).
The accuracy of the IHVDPS in assessing the presence and severity of coronary stenoses was established by comparing the measurements of IHVDPS in a control group with the measurements obtained in arteries with ≥30% diameter stenosis. The possibility of estimating the pressure at zero flow (P_{r=0}) from the extrapolation of the instantaneous diastolic velocity-pressure relation was also tested in nine cardiac transplant recipients by inducing a controlled prolonged diastolic cardiac arrest.

### Methods

#### Patient Population

**Group 1 (Normal Arteries or Arteries With <30% Diameter Stenosis; n=64)**

This group included patients undergoing coronary angiography because of suspected coronary artery disease (n=15), patients who received percutaneous coronary interventions in an artery different than the studied vessel (n=40), and asymptomatic cardiac transplant recipients undergoing control follow-up coronary angiography 1 to 5 years after transplantation (n=9). Age, sex, clinical characteristics, and type of artery studied for the patients undergoing a successful assessment are indicated in the Table. The studied arteries were examined by two experienced angiographers and classified as normal (smooth regular contours, n=29) or having minimal wall irregularities (n=34). The absence of ≥30% diameter stenosis was confirmed, when necessary, using a quantitative angiographic technique described below. In no cases did angiographically visible collaterals originate from the studied artery or was there evidence of a previous myocardial infarction or of impaired wall motion with left ventriculography in the territory of distribution of the studied artery. None of the cardiac transplant recipients had angiographically visible signs of small coronary vessel disease. Thirty-eight patients of this group (59%) were receiving antianginal and/or antihypertensive treatment at the time of the study.

**Group 2 (Arteries With ≥30% Diameter Stenosis; n=31)**

This group included 27 patients with ≥50% diameter stenosis referred for a coronary intervention because of the presence of symptoms or signs of myocardial ischemia and 4 patients with ≥30% but <50% diameter stenosis undergoing a diagnostic coronary angiogram. Patients with acute myocardial infarction or arterial occlusion or subocclusion (Thrombolysis in Myocardial Infarction flow class 0 or 1) were not included in the study. Clinical characteristics and type of vessel studied in the group undergoing a successful assessment are reported in the Table. All patients of this group were receiving antianginal treatment at the time of the study.

#### Catheterization Procedure

After intravenous administration of 10 000 IU heparin and 250 mg acetylsalicylic acid, a 7F or 8F guiding catheter was advanced up to the ostium of the studied artery. The Doppler guidewire was introduced into the proximal or midsegment of the vessel to be studied (group 1) or distal to the stenosis (group 2). After optimization of the Doppler signal and 3 to 5 minutes after intracoronary injection of a bolus of 2 to 3 mg isosorbide dinitrate, baseline flow velocity and proximal coronary pressure were recorded, and a cineangiogram was performed to measure the cross-sectional area at the site of the Doppler sample volume and the geometric characteristics of
the stenosis (when present). The flow velocity measurement was then repeated during the peak effect of an intracoronary bolus injection of papaverine (8 mg, right coronary; 12.5 mg, left coronary and saphenous vein bypass graft). Care was taken to avoid impairment of flow during maximal hyperemia due to the presence of the guiding catheter in the coronary ostium. If damping occurred, the guiding catheter was withdrawn from the coronary ostium immediately after the injection of papaverine. In six cardiac transplant recipients, left ventricular and aortic pressure were measured simultaneously using a double-sensor high-fidelity pig-tail catheter (Sentron, Roden). In these cases, a previously described automated analysis system was used to measure the peak positive and negative first derivatives of the left ventricular pressure (+dP/dt and −dP/dt), the maximal velocity of left ventricular isovolumic contraction (Vmax), and the constant of isovolumic relaxation (τ). In all of the nine cardiac transplant recipients, during the phase of maximal hyperemia after papaverine injection an intracoronary bolus of 3 mg adenosine was used to induce a prolonged diastolic cardiac arrest. Ventricular pacing was used, when necessary, to restore cardiac contraction.

Quantitative Angiographic Measurements

The guiding catheter, filmed devoid of contrast medium, was used as a scaling device. A previously validated on-line analysis system operating on digital images (ACA-DCI, Philips, Eindhoven) was used during the catheterization procedure. In this system, after automatic detection of the vessel center line, a weighted first- and second-derivative function with predetermined continuity constraints is applied to the brightness profile on each scan line perpendicular to the vessel center line. In all patients, a user-defined diameter was measured at the site of the Doppler sample volume, and the corresponding cross-sectional area was calculated assuming a circular cross section. In group 2, minimal luminal diameter was measured and percent luminal diameter stenosis was calculated using an automatic interpolated technique to measure the reference diameter.

Doppler Guidewire and Flow Velocity Measurements

The Doppler angioplasty guidewire is a 0.018-in (diameter, 0.45 mm; cross-sectional area, 0.17 mm²), 175-cm-long flexible
and steerable guidewire with a floppy shapable distal end with a 12-MHz piezoelectric transducer mounted at the tip (Cardiometrics Inc). The sample volume is positioned at a distance of 5.2 mm from the transducer and has an approximate width of 2.25 mm due to the divergent ultrasound beam, so a large part of the flow velocity profile is also included in the sample volume for eccentric positions of the Doppler guidewire. After real-time processing of the quadrature audio signal, a fast-Fourier transform algorithm is used to increase the reliability of the analysis. The Doppler system calculates and displays several spectral variables on-line, including the instantaneous peak velocity and the time-averaged (mean of 2 beats) peak velocity (Fig 1A). The flow velocity measurements obtained with this system have been validated in vitro and in an animal model using simultaneous electromagnetic flow measurements for comparison. CFR was defined as the ratio between maximal flow velocity at the peak effect of the papaverine injection and that under baseline conditions.

**Instantaneous Assessment of Flow Velocity–Pressure Relation**

Continuous acquisition of the instantaneous peak Doppler flow velocity, of the pressure measured through the guiding catheter, and of the ECG was performed with a 12-bit analog-to-digital converter (DataQ Instruments) connected to a PC. ECG, proximal coronary pressure, and instantaneous peak coronary blood flow velocity were sampled at 125 Hz per channel and stored for off-line analysis (Fig 1B). With dedicated software (ACODAS, DataQ Instruments), the acquired signals were displayed in an x-y scatterplot, so that the progressive variations of the instantaneous peak flow velocity–pressure loop from baseline to hyperemia could be monitored and four consecutive cardiac cycles without recording artifacts could be selected at peak hyperemia. The diastolic interval to be analyzed was selected using as start point the maximal diastolic velocity and as end point the beginning of the phase of rapid decrease of flow velocity induced by the ventricular contraction (Fig 1C). After identification of the interval of analysis for each cycle, linear regression was used to calculate the individual IHDPVs to study the variability among different cardiac cycles. Afterward, the data of the four selected diastolic intervals were pooled, and the mean IHDPVs was calculated. The reproducibility of the measurements was tested in 10 randomly chosen cases from group 1 for which the same four cardiac cycles were independently assessed by a second observer. In 20 patients, the variability of the measurements was also assessed using an independent selection by the same observer at a 6.5-month interval of two series of four beats during the same episode of maximal hyperemia. In the six patients in whom a high-fidelity left ventricular pressure recording was available during the measurements, the IHDPVs was assessed in the same beats using the start and end points proposed by Mancini et al (20 millisecond after peak left ventricular \(-\Delta P/\Delta t\) and upstroke of \(\Delta P/\Delta t\)).

**Velocity-Pressure Relation During Controlled Diastolic Cardiac Arrest**

In 9 cardiac transplant recipients, a second injection of papaverine intracoronary was given, followed after 30 to 45 seconds by an intracoronary bolus of 3 mg adenosine (Fig 2). Using a previously introduced right ventricular pacing catheter, pacing was performed when necessary (4 cases) to restore a normal cardiac contraction. Flushing was reported by 4 of 9 patients. None of the patients complained of chest discomfort.

**Statistical Analysis**

Results are given as mean±SD. The beat-to-beat variability of the IHDPVs was calculated as the ratio between the SD and the mean of the slopes measured over four consecutive cardiac cycles. The mean±SD of the signed difference of corresponding measurements was used to test the interobserver variability (same beats), the long-term intraobserver variability (randomly selected beats), and the variability of the measurements obtained defining the diastolic interval of analysis from the flow velocity signal or from the left ventricular pressure. Covariance analysis was used in group 1 to estimate the independency of the IHDPVs from heart rate, mean diastolic arterial pressure, cross-sectional area at the site of the velocity measurements, and left ventricular ±dP/dt and \(-\Delta P/\Delta t\), \(V_{max}\), and \(\tau\). A two-tailed Student’s t test for unpaired data was performed to compare the measurements of IHDPVs in patients with and without >30% diameter stenosis. The Bonferroni adjustment for multiple comparisons was used where appropriate.

To test the linearity of the individual velocity-pressure relations during long diastolic pauses, the data were fitted with a linear and a second-order polynomial function. A relation was considered nonlinear when the coefficient of the second-order term of the polynomial fit was significant at \(P<.01\) and when the F statistic for the polynomial fit was statistically better at \(P<.01\) than the linear fit.

**Results**

**Feasibility, Reproducibility, Beat-to-Beat Variability, and Dependence on Hemodynamic Variables of Measurement of IHDPV**

**Feasibility**

Reliable, automatic detection during maximal hyperemia of the progressive decrease in peak velocity in

**Fig 3.** Plots of variability of two measurements of instantaneous hyperemic diastolic velocity-pressure relation (IHDPV) performed by the same observer during two sessions separated by a time interval of more than 6 months and with an independent selection of the cardiac cycles. Left, Linear regression analysis; right, difference between corresponding measurements plotted against the mean of the measurements. CFR indicates coronary flow reserve; DS, diameter stenosis.
mid-late diastole was obtained in 55 of 64 patients of group 1 (86%) and in 24 of 31 patients of group 2 (77%). The poor quality of the Doppler signal or the presence of multiple artifacts impairing the accuracy of the automatic analysis was the reason for exclusion in the 16 failed measurements (9 arteries [14%] in group 1 and 7 arteries [23%] in group 2).

**Variability**

**Interobserver and intraobserver.** The mean difference between measurements of IHDVPS performed independently by two observers (n=10) was 0.004±0.0001 cm·s⁻¹·mm Hg⁻¹ (observer 1 minus observer 2), equal to 2±1% of the mean of the two measurements. When different cardiac cycles in the steady state of maximal hyperemia after papaverine were chosen independently by the same observer at a 6±2-month interval (n=20), a high correlation was still present (r=0.96), with a larger dispersion of the measurements (mean±SD difference, 0.44±11%) (Fig 3).

**Beat-to-beat variability.** Beat-to-beat variability was measured in all cases and was 13±7% and 15±7% for groups 1 and 2, respectively.

**Variability of measurements using a diastolic interval defined on morphology of velocity tracing or of high-fidelity left ventricular pressure.** The IHDVPS calculated using start and end points for the definition of the diastolic interval derived from the flow velocity tracing or from the left ventricular pressure tracing (n=6) showed a mean difference of 0.009±0.005 cm·s⁻¹·mm Hg⁻¹ (measurement with interval selected on the velocity pattern minus measurement with interval selected from the left ventricular tracing), equal to 3±2%.

**Dependence on Hemodynamic and Angiographic Variables**

In group 1, IHDVPS showed no significant correlation with heart rate, mean aortic diastolic pressure, type of vessel studied, or luminal cross-sectional area at the site of the Doppler sample volume. In 6 patients from the same group in whom high-fidelity left ventricular pressure was recorded, no correlation between IHDVPS and ±dP/dt, −dP/dt, V_max, or τ was observed.

**IHDVPS in Patients With and Without Coronary Stenoses**

**Comparison Between Normal and Stenotic Group**

The patients with and without >30% diameter stenosis in the studied artery showed no significant differences in age, sex, heart rate, presence of systemic hypertension, and cross-sectional area at the site of the Doppler measurement (Table). A significantly lower mean diastolic aortic pressure was present in the stenosis group, which included 14 cases of previous myocardial infarction in the territory of distribution of the studied artery (absent in group 1, P<.00001) and a higher number of cases in whom the left anterior descending coronary artery was the vessel studied (63% versus 38% in group 1, P<.01). Maximal diastolic coronary blood flow velocity, CFR, and the IHDVPS were significantly greater in group 1 than in group 2 (Table and Fig 4). No differences in CFR or IHDVPS were present when the patients of group 1 were divided according to the presence of left ventricular hypertrophy or systemic arterial hypertension (Fig 4) and when the patients of group 2 were divided according to the presence of a previous myocardial infarction in the territory of distribution of the studied artery. In Fig 5, the individual measurements of CFR and IHDVPS are plotted. A CFR >2 and an IHDVPS >1 were present in 5 (21%) and 3 (12%) patients of group 2, respectively.

In the normal group, a CFR and an IHDVPS equal to or less than these levels were observed in 4 (7%) and 8 (14%) arteries, respectively. Using these arbitrarily defined cutoff values, CFR and IHDVPS correctly identified 79% and 88% of the arteries with ≥30% diameter stenosis and excluded the presence of a stenosis in 93% and 86% of the remaining 55 control arteries (NS). When an absolute measurement of stenosis severity was used, all except one lesion with a minimal luminal cross-sectional area <1.5 mm² had a CFR ≤2 and an IHDVPS ≤1 (Fig 5). The measurements of the two subgroups with ≤30% diameter stenosis showed a similar overlap with the stenosis group (Fig 5).

**Correlation With Minimal Luminal Cross-Sectional Area**

In group 2, both CFR and IHDVPS showed a significant correlation with minimal luminal cross-sectional area (Fig 6). Percent diameter stenosis was significantly correlated with CFR (r=-.44, P<.05) but not with the IHDVPS (r=-.39, NS).

When groups 1 and 2 were combined and correlated with the cross-sectional area of the normal arterial segment analyzed (group 1) or with the minimal luminal cross-sectional area (group 2), a significant correlation was observed for both indexes (CFR: r=.53, P<.00001; IHDVPS: r=.38, P<.002).

**IHDVPS During Long Diastolic Pauses**

In 6 of 9 heart transplant recipients (66%), the injection of 3 mg intracoronary adenosine was followed by a diastolic pause sufficiently long to induce a reduction of the minimal aortic pressure to ≤45 mm Hg. Sinus node arrest was observed in 3 patients, whereas a third-degree atrioventricular block was the cause of the arrest of the left ventricular contraction in the remaining 3 patients. Two patients were excluded from analysis because of the deterioration of the flow velocity signal in the lower pressure range.

The individual curves of the longest pauses observed in the remaining 4 patients are plotted in Fig 7. The curvilinear relation between velocity and pressure was confirmed by the analysis of the residuals after fitting a linear and a second-order polynomial equation and by
the F test, showing that the polynomial fit was better with \( P<.01 \) in 3 of 4 cases. To determine whether the curvilinear relation between velocity and pressure was present over the entire range of measurements, an automated calculation of IHDVPS was performed using linear regression over progressively smaller ranges of measurements, starting from the lowest pressure (Fig 8) and progressively increasing the lowest pressure by 1 mm Hg to a final smallest range, which included the measurements obtained in the highest 15 mm Hg pressure range (Fig 8). This series of slopes was then plotted against the corresponding lowest pressure. The results of this analysis showed that a rather constant IHDVPS was present in a pressure range >60 mm Hg (Fig 8).

Similarly, the intercept with the pressure axis showed a progressive decrease in the lower pressure range, whereas stable values were observed in the physiological pressure range.

**Discussion**

**Instantaneous Velocity-Pressure Relation for Assessment of Stenosis Severity**

**Potential Advantages of the IHDVPS**

Experimental studies have shown that the slope of the instantaneous hyperemic diastolic flow-pressure relation index is superior to CFR for the assessment of directional changes in coronary conductance because of its independence from the hemodynamic conditions at the time of assessment.\(^{16-19}\) The large modifications in preload, heart rate, aortic pressure, and cardiac contractility and the changes in basal flow velocity that occur during coronary interventions limit the possibility of obtaining reliable immediate assessment of the outcome of the procedure using CFR.\(^{8-15}\) Confirmation in humans that the IHDVPS has advantages over CFR for the evaluation of the functional changes induced by coronary interventions would require repeated measurements before and after treatment. In this first application in humans of the index proposed by Mancini et al,\(^{16-19}\) more fundamental methodological issues were addressed, such as the assessment of the feasibility and
reproducibility of the measurements and of the ability of this index to distinguish between normal and stenotic coronary arteries.

Modalities of Measurement and Methodological Problems

In the vast majority of the studied arteries, the IHDVPS could be measured. Electromagnetic interference and a low signal-to-noise ratio were responsible for the failures in the measurement of the IHDVPS. A new electromagnetic interference filter developed for this Doppler system could drastically reduce the electromagnetic interference in the last cases studied. Transducers of higher sensitivity are in the phase of clinical testing and modifications of the tracking algorithm are being developed to improve recognition of artifacts and tracking of signal. Despite a careful selection of the beats analyzed, a relatively large beat-to-beat variability was observed, probably because of respiratory changes or of beat-to-beat variations in the accuracy of the detection of the peak diastolic velocity.

The original method proposed by Mancini et al.\textsuperscript{16} required a high-fidelity measurement of the left ventricular pressure to detect the diastolic interval of interest for analysis. Measurements obtained in a small group of patients demonstrated that the simplified approach used in this study yields results similar to those obtained selecting the interval for analysis from the left ventricular pressure tracing. A second difference between our approach and the original approach of Mancini et al.\textsuperscript{16} is the use in this study of the maximal diastolic velocity as an initial point for analysis. This selection criteria have the advantage of minimizing the subjectivity of the measurement, as confirmed by the high reproducibility of the measurements. However, in the early phases of the diastolic velocity decrease a discharge of the capacitance of the artery proximal to the site of the measurement can impair the linearity of the pressure-velocity relation. A curvilinearity of the velocity-pressure relation in the initial phase of velocity decrease during diastole was a rare finding in patients with coronary artery disease but was observed in some of our transplant patients, possibly as a consequence of the higher wall compliance of the epicardial arteries of these recently transplanted hearts. To avoid this possible source of inaccuracy, it is advisable to limit the analysis to the late diastolic interval as originally proposed by Mancini et al.\textsuperscript{16-19} We are currently testing a modified program of analysis that defines an automatic start point based on a predetermined threshold of linearity of the pressure-velocity relation. Mancini et al.\textsuperscript{16-19} could independently manipulate the hemodynamic parameters in the animal model used to assess the correlation of CFR and flow-pressure slope with each hemodynamic variable. This approach was not feasible in our clinical study, which nevertheless showed no correlation between IHDVPS and hemodynamic variables at the time of assessment, suggesting that the IHDVPS is independent from the hemodynamic parameters in humans as well.

Conceptual Limitations

A substantial difference between our approach and the method originally proposed by Mancini et al.\textsuperscript{16} is the use of flow velocity instead of absolute coronary flow normalized for the myocardial mass. A disadvantage of this approach is that the velocity-pressure slope is influenced by the dimension of the artery under assessment. Since the IHDVPS varies in proportion to perfusion bed mass and CFR does not, the lack of correction for myocardial mass may explain the better correlation of CFR with simple anatomic measurements of stenosis severity. Furthermore, it is conceivable that the IHDVPS did not show a significant advantage over CFR in the comparison of normal and stenotic arteries.

In this study, however, in normal or near-normal arteries, the IHDVPS was independent of the cross-
sectional area at the site of the velocity measurement. Only a moderate decrease of mean velocity, inversely proportional to the moderate increase in total cross-sectional area, occurs from proximal to distal in the epicardial coronary arteries. The maintenance of a relatively constant flow velocity despite the changes in cross-sectional area and in perfused myocardial bed partially limits the inaccuracy consequent to the impossibility to correct for the perfused myocardial mass. The main potential advantage of the IHDVPS over CFR is in demonstrating directional changes in coronary conductance in a constant perfusion bed, irrespective of the presence of hemodynamic perturbations. Conceptually, this advantage is not jeopardized by the use of flow velocity instead of normalized flow, but the greater consistency of the IHDVPS over CFR could not be confirmed in the present study, which analyzed a single measurement before interventions, obtained in stable hemodynamic conditions.

Although the mean IHDVPS measured in normal or near-normal arteries was more than twice the mean IHDVPS measured in arteries with ≥30% diameter stenosis, the specificity of this index in the detection of ≥30% diameter stenosis remained suboptimal and did not show advantages over CFR. In the control group selected in this study, many factors can induce an abnormal flow velocity response during maximal hyperemia (age; myocardial hypertrophy; hypercholesterolemia; abnormal endothelium-dependent dilatation; structural alterations of the microvasculature due to myocardial fibrosis, systemic hypertension, or chronic rejection after cardiac transplantation). The exclusion of two of these factors (left ventricular hypertrophy and systemic hypertension) did not reduce the overlap between the “normal” (group 1A) and stenotic group, probably because of the persistance of many of the other above-listed factors in the “normal” group. Furthermore, the flow characteristics of the normal artery in the patients with an obstruction to flow in another artery could have been modified by the presence of collateral circulation or by increased compensatory myocardial contraction. Therefore, the difference between normal and diseased vessels may be underestimated. The use of normal volunteers as a control group, however, was not feasible because of the invasive nature of the measurement and was believed to be inappropriate because the distinction between normal and diseased arteries must be performed, in clinical practice, in the same population of patients with coronary atherosclerosis.

Microvascular impairment, common in patients with coronary atherosclerosis, may represent the same Achilles’ heel to the use of the IHDVPS that it has been to CFR. A different approach must be used to overcome this limitation and distinguish the two components that may limit the maximal coronary conductance: severity of an epicardial stenosis and impaired microvascular response. Gould correlated the severity of experimentally induced coronary stenoses with the changes in the transstenotic pressure gradient—flow velocity relation in dogs. With a high-fidelity pressure transducer mounted on an angioplasty guidewire in combination with a separate Doppler guidewire, this approach has been recently applied in humans. When high-fidelity prestenotic and poststenotic pressure and flow velocity signals are available, two types of relations can be used as an alternative to the

![Graphs showing velocity, conductance, and pressure](https://i.imgur.com/5z5z5z5.png)

**Figure 8.** The instantaneous hyperemic diastolic velocity-pressure relation slope (IHDVPS) (conductance) and the x intercept (pressure at zero flow [P_{x0}]) are calculated using linear regression analysis over progressively smaller ranges of measurements, starting in the lowest pressure range (A) and progressively increasing the minimal pressure up to the higher 15 mm Hg pressure range (F). The calculated IHDVPS (conductance, lower middle) and P_{x0} (P_{x}, lower right) are plotted against the lowest pressure of the sample analyzed. Note the progressive increase in the 30 to 45 mm Hg range and the more stable values at higher pressure.
IHDVPS to separate the functional characteristics of the stenosis and of the distal vascular bed: the instantaneous relation between transstenotic pressure gradient and velocity, assessing the stenosis hemodynamics as in an isolated hydraulic model, independent of the maximal hyperemic response and of the properties of the distal vascular bed; and the relation between flow velocity and poststenotic pressure, directly correlated to the conductance of the distal vasculature.14

**Instantaneous Velocity-Pressure Relation for Assessment of Zero-Flow Pressure**

The extrapolation of the pressure-flow relation during a long diastolic pause was used in the original report by Bellamy31 to assess the \( P_{t=0} \). His observation that \( P_{t=0} \) was higher than the coronary venous pressure has initiated a great deal of experimental work to better define the mechanism and the physiological and clinical importance of this phenomenon.

**Mechanisms of Regulation of the \( P_{t=0} \)**

In discussing the importance of a \( P_{t=0} \) greater than the coronary venous pressure as a determinant of coronary resistance, Bellamy32 interpreted this phenomenon as the effect of a vascular waterfall due to active vascular constriction or to the effect of a tissue pressure higher than the intravascular pressure. The lack of a direct demonstration of vascular collapse at the arteriolar level and the persistence of venous outflow after cessation of the arterial flow33 have suggested alternative mechanisms. The assessment of instantaneous changes of diastolic flow is complicated by the effect of capacitative flow due to the blood stored in the extramural coronary arteries. When flow is measured in a proximal artery, the point of cessation of flow precedes the true cessation of flow in the coronary microvasculature because of the persistence of progressive blood discharge from the epicardial and the intramyocardial capacitance. After correction for the capacitative effects, Eng et al34 calculated a \( P_{t=0} \) similar to the right atrial pressure during maximal hyperemia. Canty et al35,36 however, confirmed the persistence of a \( P_{t=0} \) during maximal hyperemia greater than venous pressure using a capacitance-free model. The presence of a large intramyocardial capacitance with long time constants for blood discharge has been proposed as an alternative model to the presence of a vascular waterfall to explain the cessation of flow in the epicardial arteries at a pressure higher than the right atrial pressure.37 Whatever mechanism is involved in the regulation of the \( P_{t=0} \), there is a consensus that the presence of an elevated \( P_{t=0} \) (≤50 mm Hg) occurs only in conditions of coronary autoregulation and that much lower pressures are present at the cessation of the arterial flow when the coronary vasculature is maximally vasodilated.38

**Morphology of Diastolic Pressure-Flow Relation**

The diastolic flow-pressure relation during maximal hyperemia was found to have an upward concavity toward the flow axis in many experimental reports.34,35,39 This curvilinearity may be explained by a discharge of blood from the upstream epicardial vessels and by a progressive increase in vascular resistance due to the pressure-dependent decrease of arterial diameter.36 If this curvilinearity is ignored or if the pressure-flow relation is not explored in the low-pressure range, falsely elevated measurements of \( P_{t=0} \) are obtained. In this study, the measurements were obtained during a long diastolic pause, with pressures at the end of the period of cardiac arrest <45 mm Hg. However, the use of flow velocity instead of flow introduced an additional bias in the estimation of the pressure-flow relation. If the arterial cross section at the site of the velocity measurement is reduced simultaneously to the reduction in flow velocity, the velocity decrease underestimates the true flow reduction. The phenomenon is relevant for flow velocity measurements obtained in the low-pressure range because a curvilinear relation between distending pressure and arterial cross section is present, with larger changes in cross section in the low-pressure range.40 Therefore, the marked curvilinearity present in the flow velocity–pressure relation at low pressures, without a positive intercept with the pressure axis, precluded the use of the flow velocity–pressure relation for the assessment of the \( P_{t=0} \). The simultaneous use of intracoronary Doppler and two-dimensional ultrasound imaging has the potential to overcome this limitation and allow the estimation of the \( P_{t=0} \) in conscious humans in the catheterization laboratory.31 In the physiological range of pressures, however, the relation between flow velocity and pressure remained linear so that linear regression appears to be applicable to estimate arterial conductance.

**Conclusions**

The instantaneous velocity-pressure relation during maximal hyperemia can be reliably assessed using intracoronary Doppler in the catheterization laboratory, is highly reproducible, has a moderate beat-to-beat variability, and is independent of the hemodynamic parameters at the time of the assessment. Under the stable hemodynamic conditions of this study, the IHDVPS and CFR had similar sensitivities and specificities in distinguishing between normal and stenotic vessels and demonstrated similar correlation with minimal luminal cross-sectional area. Further studies will be necessary to compare these two indexes before and after interventions and confirm the independency in humans of the IHDVPS from hemodynamic perturbations, a major potential advantage of this index over CFR.

The curvilinearity of the velocity-pressure relation during long diastolic pauses complicates the use of the flow velocity–pressure relation for the assessment of the \( P_{t=0} \).**Acknowledgments**

Dr Gil is the recipient of a 1994 European Society of Cardiology Training Fellowship. The contribution to the acquisition of the data of the medical, technical, and nursing staff of the Catheterization Laboratory is gratefully acknowledged. We are indebted to Dr P.N. Ruygrok, Auckland, New Zealand, for his careful review of the manuscript and to Dr N. Meneyea, Besancon, France, for his contribution to the acquisition and analysis of the data.

**References**


C Di Mario, R Krams, R Gil and P W Serruys

Circulation. 1994;90:1215-1224
doi: 10.1161/01.CIR.90.3.1215

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1994 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/90/3/1215

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/